

REMARKS

Amendments

Claims 1-21, 26 and 28-31 have been canceled, claims 22-25 and 27 have been amended, and claims 32-39 have been added. Upon entry of the amendment, claims 22-25, 27 and 32-39 will be pending. Support for the added claims can be found in the specification, for example, on page 6, lines 12-21, page 16, lines 9 through page 17, line 26; in Example 1; the Figures; and in the claims as originally filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Rejections

Rejection under 35 U.S.C. § 112, first paragraph

Claims 22-27 stand rejected as allegedly failing to comply with the enablement requirement. The Examiner argues that the claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Applicant respectfully traverses this rejection.

The Examiner questions the use of the mouse suspension model with the NTTP-1 knockout mouse for characterization of the role of NTTP1 gene in depression.

The Examiner suggests the mouse strains used in the creation of the NTTP-1 knockout mice are unsuitable for use in the mouse tail suspension model of depression. The Examiner cites Crawley *et al.*, Psychopharmacology, 132:107-124 (1997) extensively. Crawley *et al.*, 1997 provides comparison of inbred mouse strains in, and suggests suitability for, several behavioral phenotypes. Examiner paraphrases Crawley *et al.*, 1997:

For example, two strains commonly used in ES cell and knockout generation C57BL/6 and various substrains of 129 are unusual on many standard behavioral paradigms. And

such unique traits of 129 and C57BL/6 mice are a problem for interpretation of behavioral phenotypes of null mutations.

(OA mailed 11/17/2004, page 3, lines 22-24 and page 4, line 1)

In the same reference, Crawley *et al.*, 1997 points out:

There is no best strain that can be recommended across all behavioral paradigms for all null mutations. Rather, the strain is chosen for its predicted sensitivity to the null mutation.

Crawley *et al.*, 1997 page 120, paragraph 7.

In fact, throughout Crawley *et al.* "The 129 substrains and the C57BL substrains are emphasized..." (page 108, third paragraph). Crawley *et al.* recommends strain C57BL/6 for use in several behavioral tests including the complex learning Morris water task and contextual fear conditioning tests (page 110, Table 1 and paragraph 3). Crawley further states "The best choice of an inbred background on which to explore the impact of a null mutation on learning appears to be C57BL/6"(page 110, paragraph 3). In addition, "Strains with poor prepulse inhibition, including C57BL/6J..., can be used to improve prepulse inhibition" (as a model of schizophrenia; page 112, paragraph 6).

Although Crawley *et al.*, 1997 suggests suitable mouse strains for creation of knockout mice for use in several behavioral tests, Crawley makes mention of the mouse tail suspension test, nor any mouse model of depression, let alone strain suitability for those tests, rendering Examiner's point on strain suitability irrelevant for this test.

In fact, similar mouse strains used in the creation of the NTTP-1 knockout mice (i.e. 129 ES cells and C57BL/6 mice), were used by Heisler *et al.*, *Proc. Nat. Acad. Sci. USA* 95:15049-15054 (1998) to generate 5-HT_{1A} receptor-mutant mice. The homozygous 5-HT_{1A} receptor-mutant mice of Heisler *et al.* exhibited antidepressant-like responses in the six minute tail suspension assay.

The Examiner further questions enablement of the specification with respect to the mouse suspension model used with the NTTP-1 knockout mouse for characterization of the role of NTTP1 gene in depression. The instant application describes comparison of NTTP-1 phosphatase homozygous mutant mice (-/-) with age, sex and strain matched wild-type mice (+/+) in the six minute tail suspension test as a model of depression:

Specifically, homozygous mutant (-/-) male mice (n = 12) were more active during the six-minute tail-suspension test than their wild-type (+/+) male counterparts (n = 11),

resulting in a decrease of up to about 20%-50% in immobility time, suggesting that the mutants are less prone to depression-like behavior (i.e., an anti-depressive phenotype). On average, homozygous mutants had a total immobile time of 97.49 seconds, compared to 140.53 seconds for wild-type control mice, representing a decrease of about 30% in total immobile time.

(specification, page 48, lines 18-27)

One skilled in the art would recognize how to perform the tail suspension test as a mouse model of depression given both the specification, page 19, lines 20-29 and page 48 lines 18-27, and a plethora of available references (copies attached):

1. Ferrari, F., M. Cassinadri, P. L. Tartoni, and A. Tampieri. 1991. Effects of B-HT 920 in the tail-suspension test. *Pharmacol Res* 24:75-81;
2. Ferrari, F., and D. Giuliani. 1997. Effects of (-)eticlopride and 7-OH-DPAT on the tail-suspension test in mice. *J Psychopharmacol* 11:339-44;
3. Heisler, L. K., H. M. Chu, T. J. Brennan, J. A. Danao, P. Bajwa, L. H. Parsons, and L. H. Tecott. 1998. Elevated anxiety and antidepressant-like responses in serotonin 5-HT_{1A} receptor mutant mice. *Proc Natl Acad Sci U S A* 95:15049-54;
4. Nomura, S., H. Okada, R. Naruse, and K. Yamaoka. 1991. The tail suspension test for screening antidepressant drugs: comparison of movement in ICR and NMRI mice. *Jpn J Psychiatry Neurol* 45:113-4;
5. Porsolt, R. D., R. Chermat, A. Lenegre, I. Avril, S. Janvier, and L. Steru. 1987. Use of the automated tail suspension test for the primary screening of psychotropic agents. *Arch Int Pharmacodyn Ther* 288:11-30;
6. Steru, L., R. Chermat, B. Thierry, and P. Simon. 1985. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology* 85:367-70;
7. Steru, L., R. Chermat, B. Thierry, J. A. Mico, A. Lenegre, M. Steru, P. Simon, and R. D. Porsolt. 1987. The automated Tail Suspension Test: a computerized device which differentiates psychotropic drugs. *Prog Neuropsychopharmacol Biol Psychiatry* 11:659-71;
8. Thierry, B., L. Steru, P. Simon, and R. D. Porsolt. 1986. The tail suspension test: ethical considerations. *Psychopharmacology* 90:284-5;
9. Crawley "What's wrong with my mouse?: behavioral phenotyping of transgenic and knockout mice", Wiley-Liss, N.Y., N.Y. 2000 pages 194-195.

The six minute mouse tail suspension test was developed by Steru *et al.* twenty years ago as a new method for screening antidepressants in mice (Steru *et al.*, 1985). Mice, when suspended by the tail, will alternate between active attempts at escape and immobility. The tail suspension test was deemed an ethical improvement over another mouse "behavioral despair" test, the forced swimming test which involved placing the animal in a cylinder of tepid water (Thierry *et al.*, 1986). The mouse tail suspension test was automated and computerized in 1987 (Steru *et al.*, 1987). The mouse tail suspension test has been used to test several classes of antidepressant compounds: tricyclic antidepressants including Imipramine, Desipramine, Amitriptyline, Imipramine methiodide (Nomura *et al.*, 1991); atypical antidepressants including Mianserin, Viloxazine, Nomifensine (Steru *et al.*, 1985); monoamine oxidase inhibitors including Clorgyline (Steru *et al.*, 1987); α_2 -adrenoreceptor agonists including clonidine α_2 -adrenoreceptor antagonists including yohimbine and the test drug "B-HT 920"(Ferrari *et al.*, 1991). The mouse tail suspension test was also used to implicate a dopaminergic abnormality in impaired central amine transmission underlying depression (Ferrari *et al.*, 1997).

In each cited reference above, the tail suspension test measured total immobility time over a period of six minutes as described in the application, page 48, lines 18-27. In fact, the mouse tail suspension model of depression is so well known in the art that commercially available equipment may be used to perform the test, for instance MED Associates MED-TSS-MS Complete single station tail suspension starter package; MED-TSS-300 Tail suspension add-on package and associated software SOF-821 Mouse Tail Suspension software (see e.g. www.med-associates.com).

Applicant submits that one skilled in the art would have been enabled by the specification to perform the mouse tail suspension test as a model of depression.

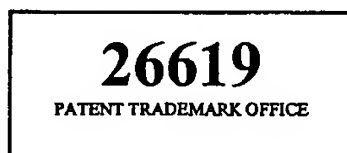
Withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

1-13-05
Date



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F:02 J:

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In re Application of: Allen, Keith D.

For: Transgenic Mice Containing NTTP1 Phosphatase Gene Disruptions

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Serial No.: 10/005,858

Filed: December 4, 2001

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Date Mailed: January 13, 2005

- ☒ Transmittal Sheet in duplicate containing Certificate of Mailing
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